Targeted Immunotherapy For Deadly Prostate Cancer Shows Promise

Antibody-drug conjugate could be a step toward selective treatment for neuroendocrine prostate cancer.

November 18, 2020 By Sabrina Richards

Using a targeting molecule to concentrate toxic chemotherapy in tumors could hold potential as a treatment for an aggressive subtype of advanced prostate cancer, according to work published November 16 in the journal Clinical Cancer Research. Scientists at Fred Hutchinson Cancer Research Center show that some neuroendocrine prostate cancer cells have high levels of a specific protein marker, and that using this marker to guide chemotherapy to these cancer cells eradicates human tumors growing in mice.

“We’re developing a targeted treatment for a disease that otherwise didn’t have any targeted treatments. That’s huge,” said Hutch prostate cancer researcher Dr. John Lee, the paper’s senior author. “It takes into account that not all cancers of a specific tissue are the same. You really have to delve deeper to understand how one person’s disease may be different from another’s.”

He is working with Immunomedics, Inc., the manufacturer of the experimental therapy and now a subsidiary of Gilead Sciences, Inc., to initiate an early stage clinical trial in patients with neuroendocrine prostate cancer. Lee and his team have no financial stake in the potential treatment.

The experimental drug is an antibody-drug conjugate, in which a drug is attached to an antibody, a specialized immune protein that can bind to other proteins. Scientists have modified them to carry cancer-killing drugs to specific cellular targets.

Neuroendocrine prostate cancer: A growing threat

Neuroendocrine prostate cancer, or NEPC, makes up about 20% of advanced, treatment-resistant prostate cancer cases, and its incidence is on the rise. Many cases of prostate cancer are treatable with surgery and radiotherapy. In its initial stages, the cancer’s growth and survival requires signaling through the tumor cells’ androgen receptor, which responds to hormones like testosterone. This makes androgen-deprivation therapies, which block testosterone and related hormones, a potent weapon against disease that isn’t cured by surgery or chemotherapy.

In the last few decades, such therapies have dramatically extended lifespan for men whose cancer recurs or resists initial forms of treatment. But they're not a cure. Eventually, prostate tumors develop resistance to anti-androgen therapies and evolve ways to continue growing and spreading without the androgen receptor. Some tumors do this by taking on molecular characteristics common to neuroendocrine cells, which are cells that interact with nerve cells to release hormones. (We naturally have neuroendocrine cells in various areas of the body, including the lungs, the pancreas and, more rarely, in the prostate.)

This presents patients, oncologists and prostate cancer researchers with a new problem.

"Neuroendocrine prostate cancer is a growing problem because there really aren't many effective therapies," Dr. Diana DeLucia, the postdoctoral fellow in Lee's lab who spearheaded the work. "So we need to develop novel ways to target tumors of patients that have neuroendocrine prostate cancer."

Lee had previously shown that some neuroendocrine prostate cancer cells, unlike cells in most tissues, produce high levels of a molecule called CEACAM5, which they carry on their surface. This suggested that CEACAM5 could act as a homing beacon to selectively guide treatments to neuroendocrine prostate tumors.

Human NEPC tumors in mice respond to targeted treatment

DeLucia continued to dig into CEACAM5 levels in neuroendocrine prostate tumor cells. She confirmed Lee's findings and also discovered that neuroendocrine prostate cancer cells that have high levels of CEACAM5 generally have low levels of different molecules that other scientists have seen to be enriched in other types of prostate cancer for which treatments are currently in development.

"It really highlights that these specifically CEACAM5-positive neuroendocrine tumors might not be captured or targeted effectively by a lot of the current strategies that are being investigated and that are in use in the clinic," she said.

DeLucia then tested whether CEACAM5 would work as a marker to guide a cancer-killing drug to NEPC cells. She and Lee chose to test an antibody-drug conjugate called labetuzumab govitecan, which is already in trials for people with colorectal cancer that have high levels of CEACAM5. DeLucia and Lee are the first to test labetuzumab govitecan in prostate cancer.

"We were focused on redirecting a therapeutic that is already being investigated in clinical stage, because that would accelerate therapeutic development," Lee said.

DeLucia tested the effects of the antibody-drug conjugate directed at CEACAM5 in preclinical models of prostate cancer in which tumor tissue taken from patients is grown in mice, also known as xenografts. She tested labetuzumab govitecan against xenograft tumors taken from four different neuroendocrine prostate cancers and found that it cleared all the tumors.

“In my opinion, we discovered a really promising potential therapeutic for neuroendocrine prostate cancer,” DeLucia said, adding that this antibody-drug conjugate may also hold promise for other tumors that express CEACAM5. Her findings are just the first step toward demonstrating that the experimental therapy works against neuroendocrine prostate cancer in people. It must be shown effective against the disease through several rounds of rigorous clinical testing.

Toward a deeper understanding of CEACAM5 in prostate cancer

Lee and DeLucia are working with the company that makes labetuzumab govitecan, Immunomedics, to set up an early-stage clinical trial to test the drug in patients with neuroendocrine prostate cancer. The Phase 1/2 trial will be designed to evaluate the safety, side effects and best dose of the treatment. Before receiving F.D.A. approval, the experimental therapy will also need to produce results in larger clinical trials designed to measure its efficacy in NEPC.

They’re also hoping to learn more about what role CEACAM5 may be playing in prostate cancer. In this study, DeLucia found that CEACAM5 pushed the tumors growing in mice to take on neuroendocrine characteristics, suggesting that CEACAM5 is doing more than merely marking some NEPC tumors. She also discovered more about how CEACAM5 gets turned on in these cells.

The researchers’ next goals are to better understand exactly what CEACAM5 is doing in NEPC and how it may be shaping neuroendocrine tumors’ behavior. They would also like to identify biomarkers associated with different neuroendocrine tumors subsets in order to more easily and more accurately monitor how well a given treatment is working in each patient.

“Not all cancers are the same — and not all neuroendocrine prostate cancers are the same,” Lee said. “It turns out there are different subsets of [NEPC], and it’s really critical for us to delve deep and understand the [genetic and molecular] drivers of these subsets.”

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